PATENT
Customer No. 22,852
Attorney Docket No. 08702.0071-00000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
Hyun KIM *et al.*	Group Art Unit: 1651
Application No.: 09/687,281	Examiner: Jennifer I. Harle
Filed: October 13, 2000	
For: INJECTABLE CARRIER FORMULATIONS OF HYALURONIC ACID DERIVATIVES FOR DELIVERY OF OSTEOGENIC PROTEINS	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

SECOND DECLARATION OF DR. HYUN KIM UNDER 37 C.F.R. § 1.132

I, Hyun Kim, do hereby make the following declaration:

1. I am an inventor of the above-captioned application. My curriculum vitae is attached to this declaration as Exhibit 1.

2. I was a graduate student at Brown University from 1994 to 1997 under the supervision of Robert Valentini. In 1997, Dr. Valentini and I filed a patent application directed to Hyaluronan Based Biodegradable Scaffolds for Tissue Repair, which issued as United States Patent 5,939,323 ("Valentini").

3. I am currently employed as a Principal Research Scientist in the Discovery Research, Drug Delivery Group at Wyeth Research in Cambridge, MA. My field of expertise is the formulation and development of novel drug delivery systems and

biomaterial carriers for proteins and drugs. I have specific expertise in the formulation of injectable and implantable carriers for drugs and in the analysis of drug interactions.

4. I have read the Office Action dated October 19, 2004, and I understand that Examiner concludes that the disclosure of the Valentini patent, when read in light of U.S. Patent Nos. 3,955,719 ("Pheulpin"), 4,784,055 ("Langen"), and 4,758,233 ("Phillips"), renders claims 1-5, 7, 11-13, 17-18, and 20-27 obvious to those skilled in the art as of the filing date of the instant application and that the disclosure of these four patents in combination with U.S. Patent No. 6,187,742 ("Wozney") renders claims 6, 15, and 19 obvious to those skilled in the art as of the filing date of the instant application.

5. I believe that those skilled in the art would not consider the injectable formulations disclosed and claimed in the pending application to be obvious modifications of the methods and compositions described in Valentini. I also believe that those of skill in the art would not consider the other cited references applicable to the invention described in Valentini.

6. In a Declaration filed on June 4, 2003, I stated that "the liquid intermediate of Valentini is not injectable because it requires a porosity of 60-90%." (Kim Declaration, ¶10.) I understand that the Examiner believes that liquids do not have porosity, only solids do. My statement was intended to refer to the porosity that results from removal of the pore formers in the intermediate during production of the final solid scaffold. In order to achieve the requisite porosity of the final scaffold, it is necessary for the liquid intermediate to contain significant amounts of pore formers, such as NaCl. Specifically, the ratio of pore formers to hyaluronic acid ester must be at least a 9:1 to achieve the final porosity of 60 to 90% in the solid scaffold of Valentini.

7. These high levels of pore formers in the intermediate composition described in Valentini render that composition uninjectable for two reasons. First, the composition comprises a thick slurry of hyaluronic acid ester, NaCl, and solvent that will not physically fit through a needle for injection through the skin of a patient. If placed into a syringe with a needle small enough to pierce the skin of a patient, a phenomenon known as filter pressing will occur. The pressure of the syringe will cause the phases to separate, and the only material that will come out of the needle will be the solvent. The hyaluronic acid, BMPs, and pore former will precipitate and remain inside the syringe barrel.

8. Second, the levels of NaCl (or any other suitable pore former) are so high in the intermediate composition that it is unacceptable for pharmaceutical uses. As I stated in my prior declaration, the levels of pore formers in the Valentini intermediate composition are superphysiological. This means that if the Valentini intermediate is administered to a patient, it will cause tissue damage. The high levels of pore formers in the Valentini intermediate will alter the transport of ions into and out of cells, resulting in inflammation, apoptosis, and cell toxicity if inserted into a patient. Accordingly, the levels of pore formers present in the Valentini compositions are not appropriate for delivery to a patient, either by injection or implantation.

9. Thus, as I stated in my declaration of June 4, 2003, removal of the pore formers from the Valentini intermediate is required before the composition is suitable for implantation into humans or animals. The process of removal requires phase reversal with a nonsolvent such as water. Neither hyaluronic acid esters nor BMPs are soluble

in water. Accordingly, the phase reversal results in the production of a solid scaffold. This solid scaffold cannot be injected through the skin of a patient.

10. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 3/17/05 By: _____

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Summary

A **scientist** and **manager** with 8 years pharmaceutical and biotechnology industry experience (10 years total) whose key roles and accomplishments include:
• Leading and participating in numerous project teams from drug discovery to preclinical R&D as drug delivery group head with 4 direct reports
• Approvals for PMA (rhBMP-2 implantable) and IND (rhBMP-2 injectable) in medical devices and biologics
• Managing internal projects and external collaborations to develop novel polymer drug delivery systems, formulation development for proteins, protein-drug conjugates for targeted drug delivery, and target ID and validation for tissue repair and regeneration (bone-tendon-cartilage repair and osteoporosis)
• Developing strategic research plan and vision, leading group and project team meetings, ensuring timely submission of intellectual property applications and/or publications, and contributing to regulatory filings

Professional Experience

Principal Research Scientist - Group Head Dec. 03 – Present
Discovery Research, Women's Health and Bone
Wyeth, Cambridge, MA
• Managed multiple projects from discovery to development using novel drug delivery systems for tendon repair and fracture repair
• Lead the conjugate program for osteoporosis as project and team leader
• Lead a team of 4 scientists as drug delivery group head
• Lead the formulation (e.g., stability, solubility), characterization (e.g., functional, cell-based, biochemical assay development) and analytical development (e.g., NMR, LC/MS, IR, GPC, DSC) of new drug entities, as well as their target identification and validation efforts (HTS assay development)
• Initiated and maintained various industrial collaborations, contracts, alliances, and business development activities with biotech / drug delivery companies
• Lead and participated in global development teams for projects in clinical development

Staff Scientist II - Group Leader Dec. 00 – Oct. 03
Discovery Research, Women's Health and Bone
Wyeth, Cambridge, MA
• Lead a team of 2 scientists as group leader
• Developed protein-small molecule conjugates and PEGylated proteins as systemic targeted therapy for osteoporosis
• Lead the injectable fracture repair program from discovery to development to clinical as core team member
• Effort resulted in one IND filing for injectable (biologic) fracture repair
• Developed injectable proteins as drug delivery formulations for local osteoporosis therapy and tendon repair
• Performed various in vitro cell-based assays, biomaterial /protein characterization tests, manufacturing feasibility tests, analytical assays, stability studies, and in vivo biodistribution / efficacy (PK/PD) studies in small and large animal models
• Initiated and managed multiple external collaborations, contracts, alliances, and business development activities with biotech / drug delivery companies
• Participated in global development team meetings and multi-functional core team meetings

• Acted as University of Washington Engineered Biomaterials key contact person

Staff Scientist I Nov. 97 – Dec. 00
Preclinical R&D, Musculoskeletal Sciences
Wyeth, Cambridge, MA
Formerly Genetics Institute, Inc.
• Developed new injectable and implantable biomaterials and drug delivery systems for bone morphogenetic proteins involved in bone and cartilage repair that resulted in one PMA for implantable (device) fracture repair.
• Developed and formulated candidate natural polymers, synthetic polymers, ceramics as local drug delivery systems for cartilage, fracture, and dental repair programs
• Performed various in vitro tests for biomaterial characterization, protein bioactivity, stability, and in vivo pharmacokinetics / biodistribution
• Evaluated pharmacodynamics of candidate biomaterial devices in small and large animal surgical models for bone and cartilage repair
• Initiated and maintained various industrial collaborations, contracts, alliances, and business development activities with biotech / drug delivery companies
• Participated in team meetings and scientific advisory board meetings

Graduate Research Assistant Sept. 94 – Oct. 97
Artificial Organs, Biomaterials, and Cellular Technology Program, Brown University
• Performed doctoral thesis research as part of research and teaching assistantship
• Gained expertise in tissue engineering, biomaterials, polymer science, drug delivery, and animal surgery
• Directed, trained, and advised over 5 undergraduate indepenent project students and 3 masters level students on different projects

Research Engineer May 92 – Aug. 94
Bioengineering Research Laboratory
Department of Orthopaedics, Rhode Island Hospital, Brown University School of Medicine
• Performed orthopedic research in bone cell biology, cytokine effects, and bone/cartilage/soft tissue biomechanics

Education

Ph.D. Medical Science, Oct 1997
Brown University, Providence, RI
Artificial Organs, Biomaterials, and Cellular Technology Program
Dept. of Molecular Pharmacology and Biotechnology
Thesis: Polymeric delivery systems and scaffolds for bone growth and morphogenetic factors
Thesis Advisor: Robert Valentini, MD, PhD

Sc.M. Biomedical Engineering, May 1992
Brown University
Thesis: Ultrasonic and mechanical characterization of cortical bone

Sc.B. Biomedical Engineering, May 1991
Brown University
Thesis: Electromyogram instrumentation design

M.S Project and Program Management, Currently Enrolled
Brandeis University
Rabb School of Continuing Education

Fields of Expertise

- Project Management/MS Project
- Tissue Engineering
- Musculoskeletal tissue repair and regeneration
- Drug Delivery Systems and Biomaterials
- Formulation Development
- Bioconjugation / PEGylation
- Target ID/Validation
- Drug Efficacy and Safety Assessment
- Assay Development / Stability
- Pharmacokinetics
- Analytical and Cell Based Assays
- Animal Surgery - in vivo animal models

Selected Publications in Scientific Journals

Kim HD, Wozney JM, Li RH (2004). Characterization of a calcium phosphate-based matrix for rhBMP-2. *Methods Mol. Biol.* 238:49-64.

Seeherman H, Bouxsein M, **Kim HD**, Li RH, Li X, Aiolova M, Wozney J (2003). A single injection of rhBMP-2/calcium phosphate cement accelerates osteotomy healing in nonhuman primates compared to other injectable carriers. *J Bone Joint Surg.* (submitted).

Li RH, Bouxsein M, Blake C, D'Augusta D, **Kim HD**, Li X, Wozney J, Seeherman H (2003). RhBMP-2 injected in a calcium phosphate paste (alpha-BSM) accelerates healing in the rabbit ulnar osteotomy model. *J Ortho Res.* 21:997-1004.

Kim HD and Valentini RF (2002). Retention and activity of BMP-2 in hyaluronic acid-based scaffolds in vitro. *J Biomed Mater Res.* 59:573-584.

Payumo FC, **Kim HD**, Sherling MA, Smith LP, Powell C, Wang X, Keeping HS, Valentini RF, Vandenburgh HH (2002). Tissue engineering skeletal muscle for orthopaedic applications. *Clin. Orthop.* 403: S228-S242.

Kim HD and Valentini RF (1999). Protein therapeutics for skeletal tissue repair. *Encyclopedia of Controlled Drug Delivery*, Mathiowitz E (ed.), Wiley and Sons, New York, 1999, p.889-895.

Sellers RS, Zhang R, Glasson SS, **Kim HD**, Peluso D, Beckwith K, and Morris EA (1999). Articular cartilage defect repair one year following treatment with rhBMP-2. *J. Bone Joint Surg. Am.* 82(2): 151-60.

Kim HD, Smith JS, Valentini RF (1998). Bone morphogenetic protein-2 coated PLLA scaffolds: release kinetics and induction of pluripotent C3H10T1/2 cells. *Tissue Engineering* 4: 35-51.

Kim HD and Valentini RF (1997). Human osteoblast response in vitro to PDGF and TGFβ delivered from controlled release polymer rods. *Biomaterials* 18: 1175-1184.

Swartz SM, Groves MS, **Kim HD**, Walsh WR (1996). Mechanical properties of bat wing membrane skin. *Journal of Zoology* 239: 357-378.

Walsh WR, **Kim HD**, Jong YS, Valentini RF (1995). Controlled release of platelet-derived growth factor using ethylene vinyl acetate copolymer (EVAc) coated on stainless-stell wires. *Biomaterials.* 16: 1319-1325.

Walsh WR, Labrador DP, **Kim HD**, Guzelsu N (1994). The effect of in vitro fluoride ion treatment on the ultrasonic properties of cortical bone. *Annals of Biomedical Engineering* 22: 404-415.

Walsh WR, Olmedo M, **Kim HD**, Zou LJ, Weiss APC (1994). Human osteoblast response to PTFE surfaces. *Clinical Materials* 16: 201-210.

Walsh WR, Labrador DP, **Kim HD**, Guzelsu N (1994). Ultrasonic properties of cortical bone following in vitro fluoride ion treatment. *Hydroxyapatite and Related Materials*, Eds. Brown P and Constantz B, CRC Press, 311-317.

Walsh WR, **Kim HD**, Labrador DP, Guzelsu N (1994). Mineral-organic interfacial bonding: effect of strain rate on the mechanical properties of bone. *Hydroxyapatite and Related Materials*, Eds. Brown P and Constantz B, CRC Press, 289-293.

Kim HD, Walsh WR (1993). Mechanical and ultrasonic characterization of cortical bone. *Biomimetics* 1(4): 293-310.

Kim HD, Harry JD, Walsh WR (1993). Ultrasonic characterization of cortical bone versus position and orientation. *Journal of Biomechanics* 26(3): 287.

Selected Abstracts and Presentations

Kim HD, Seeherman H, Wozney J, Li R (2003). Injectable rhBMP-2 delivery systems for osteoporosis. Proceedings, GRIBOI Conference, Baltimore, Maryland.

Kim HD, D'Augusta D, Zoltan A, Payumo F, Seeherman H, Li J, Wozney J, Li R (2002). Intraosseous delivery of rhBMP-2/hyaluronan for osteoporosis. 29th Annual Meeting of the Controlled Release Society, Seoul, Korea.

Glasson S, **Kim HD**, Li R, D'Augusta D, Morris E (2001). In vitro protein release kinetics may not predict in vivo release. Accepted, 4th Combined Meeting of Orthopaedic Research Society, Greece.

Kim HD, D'Augusta DA, Li RH (2000). Formulation of hyaluronic acid ester-based injectable carriers for the delivery of rhBMP-2. Transactions, Sixth World Biomaterials Congress, Hawaii, p.626.

Kim HD, D'Augusta DA, Li RH, Seeherman H, Li J, Wozney J (2000). Biodistribution and efficacy of rhBMP-2 delivered in injectable hyaluronic acid esters. Transactions, Sixth World Biomaterials Congress, Hawaii, p.1398.

D'Augusta DA, McCarthy K, **Kim HD**, Li RH (2000). Methods for in vitro characterization of rhBMP-2 carriers. Transactions, Sixth World Biomaterials Congress, Hawaii, p.1254.

Li RH, Seeherman H, Bouxsein M, D'Augusta DA, Blake C, Ammirati K, Luppen C, Stevens M, Li J, **Kim HD**, Wozney J (2000). Acceleration of fracture healing with rhBMP-2 delivered in an injectable Gelfoam delivery system. Transactions, Sixth World Biomaterials Congress, Hawaii, p.560.

Kim HD, D'Augusta DA, Li R, Bouxsein M, Blake C, Ammirati K, Luppen C, Seeherman H., Li J, Stevens M, Golden J, Wozney J (1999). Biodistribution and efficacy of rhBMP-2 in hyaluronan based carriers. Proceedings of the 26th Symposium of Controlled Release Society, Boston, MA. p.100.

D'Augusta DA, **Kim HD**, Seeherman, Li J, Golden J, Blake C, Ammirati K, Ciarametaro P, Bryant L, DeVore D, Wozney J (1999). Ectopic bone formation and in vivo retention of recombinant human bone morphogenetic protein-2 in an injectable collagen matrix. Transactions of the 25th Annual Meeting, *Society for Biomaterials*, Providence, RI, 22: 259.

Glasson SS, **Kim HD**, D'Augusta DA, Morris EA (1998). BMP-2 delivery in rabbit full-thickness cartilage defects. 2nd Symposium of International Cartilage Repair Society, Boston, MA.

Kim HD, Ferris DM, Valentini RF (1998). Sustained polymeric delivery of rhBMP-2 does not induce ectopic bone in vivo. Transactions of the 24th Annual Meeting, *Society for Biomaterials*, San Diego, CA, 21: 148.

Kim HD, Smith JS, Valentini RF (1997). Bone morphogenetic protein-2 induction of pluripotent C3H10T1/2 cells in porous PLLA scaffolds. Transactions of the 43rd Annual Meeting, *Orthopedic Research Society*, San Francisco, CA, 22: 546.

Kim HD and Valentini RF (1997). Degradable scaffolds containing bone morphogenetic protein-2 for skeletal tissue engineering. 11th World Congress of the International Society for Artificial Organs, Providence, RI. *Artificial Organs* 21: 492.

Smith LP, Jong, YS, Zielinski BA, **Kim HD**, Okun LE, Valentini RF (1997). Evaluation of human osteosarcoma cell: induction of pluripotent C3H10T1/2 cells in vitro. 11th World Congress of the International Society for Artificial Organs, Providence, RI. *Artificial Organs* 21: 498.

Sherling M, Zou L, Moodie G, **Kim HD**, Okun L, Ehrlich M., Valentini RF (1997). Peptides coupled to polymer membranes enhance osteoblast differentiation in vitro. 11th World Congress of the International Society for Artificial Organs, Providence, RI. *Artificial Organs* 21: 497.

Kim HD, Valentini RF (1997). Enhanced retention of rhBMP-2 by porous scaffolds fabricated from derivatized hyaluronic acid. Transactions of the 23rd Annual Meeting, *Society for Biomaterials*, New Orleans, LA, 20: 347.

Valentini RF, Toomay SM, **Kim HD**, Ahmed S, Sheldon B (1997). Void volume, biodegradation and tissue ingrowth parameters of hyaluronic acid-based 3-D scaffolds. Transactions of the 23rd Annual Meeting, *Society for Biomaterials*, New Orleans, LA, 20: 28.

Payumo F, **Kim HD**, Sherling M, Smith L, Keeping H, Valentini RF, Drozdoff V, Vandenburgh H (1997). Expression of recombinant human bone morphogenetic protein-6 in C2C12 myoblasts. 11th World Congress of the International Society for Artificial Organs, Providence, RI. *Artificial Organs* 21: 496.

Kim HD, Valentini RF (1996). Hyaluronan based biodegradable scaffolds for skeletal tissue reconstruction. *Transactions, 5th World Biomaterials Congress*, Toronto, Canada, 2: 236.

Kim HD, Gilheeney SW, Valentini RF (1995). Development of a drug delivery system for sequential or concurrent release of growth factors. Transactions of the 21st Annual Meeting, *Society for Biomaterials*, San Francisco, CA, 18: 188.

Valentini RF, Zou L, **Kim HD** (1995). Increased osteocalcin synthesis by rat calvarial osteoblasts cultured on RGD-grafted substrates. Transactions of the 21st Annual Meeting, *Society for Biomaterials*, San Francisco, CA, 18: 65.

Kim HD, Ehrlich MG, Valentini RF (1995). Effects of sequential and concurrent delivery of PDGF and TGFß on human osteoblasts in vitro. 41st Annual Meeting, *Orthopaedic Research Society*, Orlando FL.

Kim HD, Jong YS, Zou LJ, Valentini RF, Walsh WR (1994). Controlled release of bioactive PDGF to osteoblasts in vitro using an EVAc polymer drug delivery system. *Transactions, 20th Annual Meeting of the Society for Biomaterials*, Boston MA, 17: 117.

Walsh WR, **Kim HD**, Labrador DP, Christiansen DL (1994). Biomimetic development of a mineral-organic composite. *Transactions, 20th Annual Meeting of the Society for Biomaterials*, Boston MA, 17: 162.

Christiansen DL, **Kim HD**, Labrador DP, Walsh WR (1994). Transmission and scanning electron microscopic characterization of a biomimetic mineral-organic composite. *Transactions, 20th Annual Meeting of the Society for Biomaterials*, Boston MA, 17: 164.

Walsh WR, Russell MS, Steele J, Howlett R, **Kim HD** (1994). Morphological characterization of osteoblasts on different charged substrata. *Proceedings, 4th Annual Meeting of the Australian Society for Biomaterials*, Sydney.

Walsh WR, Abate J, Fadale P, Labrador D, **Kim HD** (1994). In vitro degradation of cannulated poly-lactic acid screws for ACL reconstructions. *Transactions, 20th Annual Meeting of the Society for Biomaterials*, Boston MA, 17: 308.

Groves MS, Swartz SM, **Kim HD**, Walsh WR (1994). Mechanical properties of wing membrane skin in microchiropteran bats. *Proceedings, Australian Evolutionary Biology Society*, Sydney.

Walsh WR, **Kim HD**, Guzelsu N (1993). Mineral-organic interfacial bonding: effect of strain rate on the mechanical properties of bone. *Transactions, Spring Meeting of the Materials Research Society*, San Francisco CA, 425.

Walsh WR, **Kim HD**, Labrador D, Guzelsu N (1993). Fluoride ion effects on the ultrasonic properties of bone. *Transactions, Spring Meeting of the Materials Research Society*, San Francisco CA, 424.

Kim HD, Walsh WR (1993). Mechanical and ultrasonic characterization of cortical bone. *Transactions, 19th Annual Meeting of the Society for Biomaterials*, Birmingham AL, 16: 156.

Kim HD, Harry JD Walsh WR (1992). Ultrasonic characterization of cortical bone versus position and orientation. *Proceedings of the NACOB II, The Second North American Congress on Biomechanics*, Chicago IL, 21.

Patents

- US Patent 5,939,923 Issued 1999
  Hyaluronan based biodegradable scaffolds for tissue repair
- US Patent pending (Serial number 09/687,281) 2003
  Injectable carrier formulations of hyaluronic acid derivatives for delivery of osteogenic proteins
- US Patent filed 2002
  Formulation of chemically modified rhBMP-2 carriers
- US Patent filed 2002
  Injectable solid hyaluronic acid rods for delivery of osteogenic proteins
- US Patent filed 2002
  Injectable calcium phosphate solid rods and pastes for delivery of osteogenic proteins

Societies and Activities

- American Association for the Advancement of Science (AAAS)
- Society for Biomaterials
- Orthopaedic Research Society
- Controlled Release Society